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## EXHIBIT 4

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Approved Product Information / Package Insert for  
Dutasteride soft gelatin capsules, 0.5mg  
NDA21-319

## PRODUCT INFORMATION

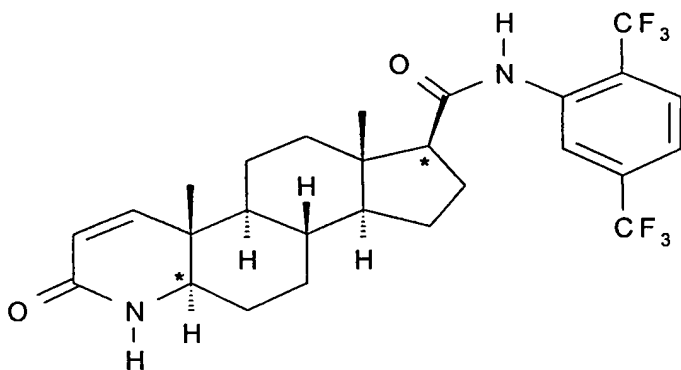
### TRADENAME

(dutasteride)

#### Soft Gelatin Capsules

**DESCRIPTION:** TRADENAME (dutasteride) is a synthetic 4-azasteroid compound that is a selective inhibitor of both the type 1 and type 2 isoforms of steroid 5 $\alpha$ -reductase (5AR), an intracellular enzyme that converts testosterone to 5 $\alpha$ -dihydrotestosterone (DHT).

Dutasteride is chemically designated as (5 $\alpha$ , 17 $\beta$ )-N-{2, 5 bis(trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is C<sub>27</sub>H<sub>30</sub>F<sub>6</sub>N<sub>2</sub>O<sub>2</sub>, representing a molecular weight of 528.5 with the following structural formula:



Dutasteride is a white to pale yellow powder with a melting point of 242 to 250°C. It is soluble in ethanol (44 mg/mL), methanol (64 mg/mL) and polyethylene glycol 400 (3 mg/mL), but it is insoluble in water.

TRADENAME Soft Gelatin Capsules for oral administration contain 0.5 mg of the active ingredient dutasteride in yellow capsules with red print. Each capsule contains 0.5 mg dutasteride dissolved in a mixture of mono-di-glycerides of caprylic/capric acid and butylated hydroxytoluene. The inactive excipients in the capsule shell are gelatin (from certified BSE-free bovine sources), glycerin, and ferric oxide (yellow). The soft gelatin capsules are printed with edible red ink.

#### CLINICAL PHARMACOLOGY:

**Pharmacodynamics: Mechanism of Action:** Dutasteride inhibits the conversion of testosterone to 5 $\alpha$ -dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland. Testosterone is converted to DHT by the enzyme 5 $\alpha$ -reductase, which exists as 2 isoforms, type 1 and type 2. The type 2 isoenzyme is primarily active in the reproductive tissues while the type 1 isoenzyme is also responsible for testosterone conversion in the skin and liver.

Dutasteride is a competitive and specific inhibitor of both type 1 and type 2 5 $\alpha$ -reductase isoenzymes, with which it forms a stable enzyme complex. Dissociation from this complex has been evaluated under in vitro and in vivo conditions and is extremely slow. Dutasteride does not bind to the human androgen receptor.

**Effect on DHT and Testosterone:** The maximum effect of daily doses of dutasteride on the reduction of DHT is dose dependent and is observed within 1 to 2 weeks. After 1 and 2 weeks of daily dosing with dutasteride 0.5 mg, median serum DHT concentrations were reduced by 85% and 90%, respectively. In patients with BPH treated with dutasteride 0.5 mg/day for 1 year, the median decrease in serum DHT was 94%. The median increase in serum testosterone was 19% but remained within the physiologic range.

In BPH patients treated with 5 mg/day of dutasteride or placebo for up to 12 weeks prior to transurethral resection of the prostate, mean DHT concentrations in prostatic tissue were significantly lower in the dutasteride group compared with placebo (784 and 5793 pg/g, respectively,  $p < 0.001$ ). Mean prostatic tissue concentrations of testosterone were significantly higher in the dutasteride group compared with placebo (2073 and 93 pg/g, respectively,  $p < 0.001$ ).

Adult males with genetically inherited type 2 5 $\alpha$ -reductase deficiency also have decreased DHT levels. These 5 $\alpha$ -reductase deficient males have a small prostate gland throughout life and do not develop BPH. Except for the associated urogenital defects present at birth, no other clinical abnormalities related to 5 $\alpha$ -reductase deficiency have been observed in these individuals.

**Other Effects:** Plasma lipid panel and bone mineral density were evaluated following 52 weeks of dutasteride 0.5 mg once daily in healthy volunteers. There was no change in bone mineral density as measured by dual energy x-ray absorptiometry (DEXA) compared with either placebo or baseline. In addition, the plasma lipid profile (i.e., total cholesterol, low density lipoproteins, high density lipoproteins, and triglycerides) was unaffected by dutasteride. No clinically significant changes in

adrenal hormone responses to ACTH stimulation were observed in a subset population (n = 13) of the one-year healthy volunteer study.

**Pharmacokinetics:**

**Absorption:** Following administration of a single 0.5-mg dose of a soft gelatin capsule, time to peak serum concentrations (T<sub>max</sub>) of dutasteride occurs within 2 to 3 hours. Absolute bioavailability in five healthy subjects is approximately 60% (range 40% to 94%). When the drug is administered with food, the maximum serum concentrations were reduced by 10% to 15%. This reduction is of no clinical significance.

**Distribution:** Pharmacokinetic data following single and repeat oral doses show that dutasteride has a large volume of distribution (300 to 500 L). Dutasteride is highly bound to plasma albumin (99.0%) and alpha-1 acid glycoprotein (96.6%).

In a study of healthy subjects (n = 26) receiving dutasteride 0.5 mg/day for 12 months, semen dutasteride concentrations averaged 3.4 ng/mL (range 0.4 to 14 ng/mL) at 12 months and, similar to serum, achieved steady-state concentrations at 6 months. On average, at 12 months, 11.5% of serum dutasteride concentrations partitioned into semen.

**Metabolism and Elimination:** Dutasteride is extensively metabolized in humans. While not all metabolic pathways have been identified, in vitro studies showed that dutasteride is metabolized by the CYP3A4 isoenzyme to 2 minor mono-hydroxylated metabolites. Dutasteride is not metabolized in vitro by human cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP2D6 at 2000 ng/mL (50-fold greater than steady-state serum concentrations). In human serum, following dosing to steady state, unchanged dutasteride, 3 major metabolites (4'-hydroxydutasteride, 1,2-dihydrodutasteride, and 6-hydroxydutasteride) and 2 minor metabolites (6,4'-dihydroxydutasteride and 15-hydroxydutasteride), as assessed by mass spectrometric response, have been detected. The absolute stereochemistry of the hydroxyl additions in the 6 and 15 positions is not known. In vitro, 4'-hydroxydutasteride and 1, 2-dihydrodutasteride metabolites are much less potent than dutasteride against both isoforms of human 5AR. The activity of 6 $\beta$ -hydroxydutasteride is comparable to that of dutasteride.

Dutasteride and its metabolites were excreted mainly in feces. As a percent of dose, there was approximately 5% unchanged dutasteride (~1% to ~15%) and 40% as dutasteride-related metabolites (~2% to ~90%). Only trace amounts of unchanged dutasteride were found in urine (<1%). Therefore, on average, the dose unaccounted for approximated 55% (range 5% to 97%).

The terminal elimination half-life of dutasteride is approximately 5 weeks at steady state. The average steady-state serum dutasteride concentration was 40 ng/mL following 0.5 mg/day for 1 year. Following daily dosing, dutasteride serum concentrations achieve 65% of steady-state concentration after 1 month and approximately 90% after 3 months. Due to the long half-life of dutasteride, serum concentrations remain detectable (greater than 0.1 ng/mL) for up to 4 to 6 months after discontinuation of treatment.

**Special Populations: *Pediatric:*** Dutasteride pharmacokinetics have not been investigated in subjects less than 18 years of age.

***Geriatric:*** No dose adjustment is necessary in the elderly. The pharmacokinetics and pharmacodynamics of dutasteride were evaluated in 36 healthy male subjects between the ages of 24 and 87 years following administration of a single 5-mg dose of dutasteride. In this single-dose study, dutasteride half-life increased with age (approximately 170 hours in men 20 to 49 years of age, approximately 260 hours in men 50 to 69 years of age, and approximately 300 hours in men over 70 years of age). Of 2166 men treated with dutasteride in the 3 pivotal studies, 60% were age 65 and over and 15% were age 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

***Gender:*** TRADENAME is not indicated for use in women (see WARNINGS and PRECAUTIONS). The pharmacokinetics of dutasteride in women have not been studied.

***Race:*** The effect of race on dutasteride pharmacokinetics has not been studied.

***Renal Impairment:*** The effect of renal impairment on dutasteride pharmacokinetics has not been studied. However, less than 0.1% of a steady-state 0.5-mg dose of dutasteride is recovered in human urine, so no adjustment in dosage is anticipated for patients with renal impairment.

***Hepatic Impairment:*** The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized, exposure could be higher in hepatically impaired patients (see PRECAUTIONS: Use in hepatic impairment).

#### **Drug Interactions:**

In vitro drug metabolism studies reveal that dutasteride is metabolized by human cytochrome P450 isoenzyme CYP3A4. In a human mass balance analysis (n = 8), dutasteride was extensively metabolized. Less than 20% of the dose was excreted unchanged in the feces. No clinical drug interaction studies have been performed to evaluate the impact of CYP3A4 enzyme inhibitors on

dutasteride pharmacokinetics. However, based on the in vitro data, blood concentrations of dutasteride may increase in the presence of inhibitors of CYP3A4 such as ritonavir, ketoconazole, verapamil, diltiazem, cimetidine, and ciprofloxacin. Dutasteride is not metabolized in vitro by human cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, and CYP2D6 at 2000 ng/mL (50-fold greater than steady-state serum concentrations).

Clinical drug interaction studies have shown no pharmacokinetic or pharmacodynamic interactions between dutasteride and tamsulosin, terazosin, warfarin, digoxin, and cholestyramine (see PRECAUTIONS: Drug Interactions)

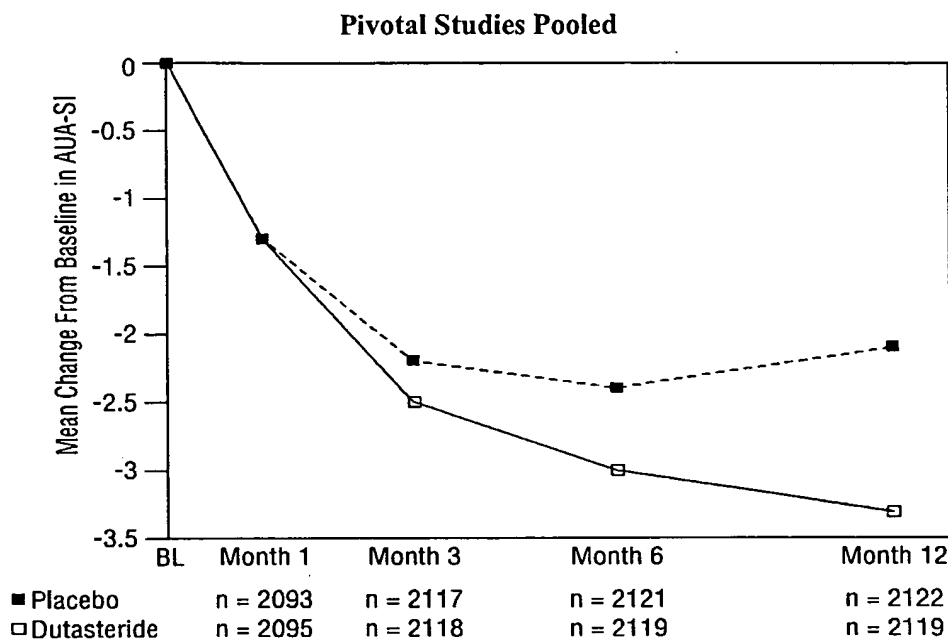
Dutasteride does not inhibit the in vitro metabolism of model substrates for the major human cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1000 ng/mL, 25 times greater than steady-state serum concentrations in humans.

**CLINICAL STUDIES:** Dutasteride 0.5 mg/day (n = 2166) or placebo (n = 2158) was evaluated in male subjects with BPH in three 2-year multicenter, placebo-controlled, double-blind studies, each with 2-year open-label extensions. Data from the first 12 months of the trials are presented. More than 90% of the study population was Caucasian. Subjects were at least 50 years of age with BPH diagnosed by medical history and physical examination, including enlarged prostate ( $\geq 30$  cc) and BPH symptoms that were moderate to severe according to the American Urological Association Symptom Index (AUA-SI). Most of the 4324 subjects randomly assigned to receive either dutasteride or placebo completed the first full year of treatment (82% and 81%, respectively).

**Effect on Symptom Scores:** Symptoms were quantified using the AUA-SI, a questionnaire that evaluates urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia) by rating on a 0 to 5 scale for a total possible score of 35. The baseline AUA-SI score across the three studies was approximately 17 units in both treatment groups.

Subjects receiving dutasteride achieved statistically significant improvement in symptoms versus placebo by Month 3 in one study, and by Month 12 in the other two pivotal studies. At Month 12, the mean decrease from baseline in AUA-SI symptom scores across the three studies pooled was -3.3 units for dutasteride and -2.1 units for placebo with a mean difference between the two treatment groups of -1.2 (range, -1.1 to -1.5 units in each of the three studies,  $p < 0.001$ ) and was consistent across the three studies. The differences between active treatment and placebo were larger in the sub-population of subjects with baseline prostate volumes of at least 40 cc.

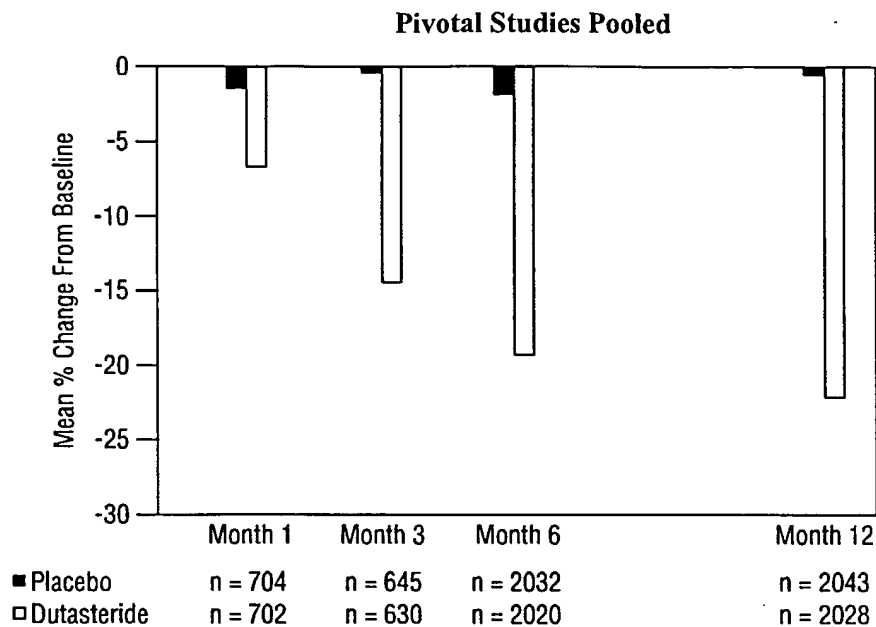
**Figure 1: AUA Symptom Score\* Change from Baseline**



\*AUA SI score ranges from 0 to 35.

**Effect on Prostate Volume:** A prostate volume of at least 30 cc measured by transrectal ultrasound was required for study entry. The mean prostate volume at study entry was approximately 54 cc.

Statistically significant differences (dutasteride versus placebo) were noted at the earliest post-treatment prostate volume measurement in each study (Month 1, Month 3, or Month 6) and continued through Month 12. At Month 12, the mean percent decrease in prostate volume across the three studies pooled was -22.2% for dutasteride and -0.5% for placebo; the mean difference (dutasteride minus placebo) was -21.7% (range, -21.1% to -22.5% in each of the three studies,  $p < 0.001$ ).

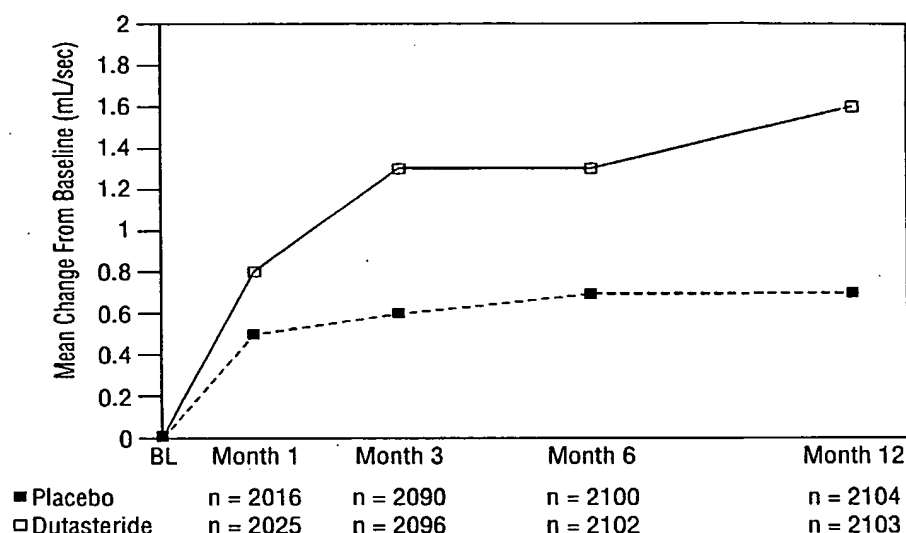
**Figure 2: Prostate Volume Percent Change from Baseline**

**Effect on Maximum Urine Flow Rate:** A mean peak urine flow rate (Q<sub>max</sub>) of ≤15 mL/sec was required for study entry. Baseline Q<sub>max</sub> was approximately 10 mL/sec at baseline across the three pivotal studies.

Differences between the two groups were statistically significant from baseline at Month 3 in all three studies and were maintained through Month 12. At Month 12, the mean increase in Q<sub>max</sub> across the three studies pooled was 1.6 mL/sec for dutasteride and 0.7 mL/sec for placebo; the mean difference (dutasteride minus placebo) was 0.9 mL/sec (range, 0.7 to 1.1 mL/sec in each of the three studies, p<0.001).



**Figure 3: Qmax Change from Baseline**  
**Pivotal Studies Pooled**



**Summary of Clinical Studies:** The data from these studies showed improvement in BPH-related symptoms, decreased prostate volume, and increased maximum urinary flow rates with dutasteride treatment.

**INDICATIONS AND USAGE:** TRADENAME is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate gland.

**CONTRAINDICATIONS:** TRADENAME is contraindicated for use in women and children. TRADENAME is contraindicated for patients with known hypersensitivity to dutasteride, other 5 $\alpha$ -reductase inhibitors, or any component of the preparation.

**WARNINGS:**

**Exposure of Women-Risk to Male Fetus:** Dutasteride is absorbed through the skin. Therefore, women who are pregnant or may be pregnant should not handle TRADENAME Soft Gelatin Capsules because of the possibility of absorption of dutasteride and the potential risk of a fetal anomaly to a male fetus (see CONTRAINDICATIONS). In addition, women should use caution whenever handling TRADENAME Soft Gelatin Capsules.

**PRECAUTIONS:**

**General:** Lower urinary tract symptoms of BPH can be indicative of other urological diseases, including prostate cancer. Patients should be assessed to rule out other urological diseases prior to treatment with TRADENAME. Patients with a large residual urinary volume and/or severely diminished urinary flow may not be good candidates for 5 $\alpha$ -reductase inhibitor therapy and should be carefully monitored for obstructive uropathy.

**Blood Donation:** Men being treated with dutasteride should not donate blood until at least 6 months have passed following their last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

**Use in Hepatic Impairment:** The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Because dutasteride is extensively metabolized and has a half-life of approximately 5 weeks at steady state, caution should be used in the administration of dutasteride to patients with liver disease.

**Use with Potent CYP3A4 Inhibitors:** Although dutasteride is extensively metabolized, no metabolically-based drug interaction studies have been conducted. The effect of potent CYP3A4 inhibitors has not been studied. Because of the potential for drug-drug interactions, care should be taken when administering dutasteride to patients taking potent, chronic CYP3A4 enzyme inhibitors (e.g., ritonavir).

**Effects on PSA and Prostate Cancer Detection:** Digital rectal examinations, as well as other evaluations for prostate cancer, should be performed on patients with BPH prior to initiating therapy with TRADENAME and periodically thereafter.

Dutasteride reduces total serum PSA concentration by approximately 40% following 3 months of treatment and 50% following 6 and 12 months of treatment. This decrease is predictable over the entire range of PSA values, although it may vary in individual patients. Therefore, for interpretation of serial PSAs in a man taking TRADENAME, a new baseline PSA concentration should be established after 3 to 6 months of treatment, and this new value should be used to assess potentially cancer-related changes in PSA. To interpret an isolated PSA value in a man treated with TRADENAME for 6 months or more, the PSA value should be doubled for comparison with normal values in untreated men.

**Information for Patients:** Physicians should instruct their patients to read the Information for Patient leaflet before starting therapy with TRADENAME and to reread it upon prescription renewal for new information regarding the use of TRADENAME.

TRADENAME Soft Gelatin Capsules should not be handled by a woman who is pregnant or who may become pregnant because of the potential for absorption of dutasteride and the subsequent

potential risk to a developing male fetus (see CONTRAINDICATIONS, and WARNINGS: Exposure Of Women—Risk To Male Fetus).

Physicians should inform patients that ejaculate volume might be decreased in some patients during treatment with TRADENAME. This decrease does not appear to interfere with normal sexual function. In clinical trials, impotence and decreased libido, considered by the investigator to be drug-related, occurred in a small number of patients treated with TRADENAME or placebo (5% and 3%, respectively, see ADVERSE REACTIONS).

Men treated with dutasteride should not donate blood until at least 6 months have passed following their last dose to prevent pregnant women from receiving dutasteride through blood transfusion (see PRECAUTIONS: Blood Donation).

#### **Drug Interactions:**

Caution should be used in administering dutasteride to patients taking potent, chronic CYP3A4 inhibitors (see PRECAUTIONS: Use with Potent CYP3A4 Inhibitors).

Dutasteride does not inhibit the in vitro metabolism of model substrates for the major human cytochrome P450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at a concentration of 1000 ng/mL, 25 times greater than steady-state serum concentrations in humans. In vitro studies demonstrate that dutasteride does not displace warfarin, diazepam, or phenytoin from plasma protein binding sites, nor do these model compounds displace dutasteride.

**Digoxin:** In a study of 20 healthy volunteers, TRADENAME did not alter the steady-state pharmacokinetics of digoxin when administered concomitantly at a dose of 0.5 mg/day for 3 weeks.

**Warfarin:** In a study of 23 healthy volunteers, 3 weeks of treatment with TRADENAME 0.5 mg/day did not alter the steady-state pharmacokinetics of the S- or R-warfarin isomers or alter the effect of warfarin on prothrombin time when administered with warfarin.

**Alpha adrenergic blocking agents:** In a single sequence, cross-over study in healthy volunteers, the administration of tamsulosin or terazosin in combination with TRADENAME had no effect on the steady-state pharmacokinetics of either alpha adrenergic blocker. The percent change in DHT concentrations was similar for TRADENAME alone compared with the combination treatment.

**Calcium Channel Antagonists:** In a population PK analysis, a decrease in clearance of dutasteride was noted when co-administered with the CYP3A4 inhibitors verapamil (-37%, n = 6) and diltiazem (-44%, n = 5). In contrast, no decrease in clearance was seen when amlodipine, another calcium channel antagonist that is not a CYP3A4 inhibitor, was co-administered with dutasteride (+7%, n = 4).

**Cholestyramine:** Administration of a single 5-mg dose of TRADENAME followed 1-hour later by 12 g cholestyramine did not affect the relative bioavailability of dutasteride in 12 normal volunteers.

**Other Concomitant Therapy:** Although specific interaction studies were not performed with other compounds, approximately 90% of the subjects in the 3 Phase III pivotal efficacy studies receiving TRADENAME were taking other medications concomitantly. No clinically significant adverse interactions could be attributed to the combination of TRADENAME and concurrent therapy when TRADENAME was co-administered with anti-hyperlipidemics, angiotensin-converting enzyme (ACE) inhibitors, beta-adrenergic blocking agents, calcium channel blockers, corticosteroids, diuretics, nonsteroidal anti-inflammatory drugs (NSAIDs), phosphodiesterase Type V inhibitors, and quinolone antibiotics.

**Drug/Laboratory Test Interactions:** Effects on PSA: PSA levels generally decrease in patients treated with TRADENAME as the prostate volume decreases. In approximately one-half of the subjects, a 20% decrease in PSA is seen within the first month of therapy. After 6 months of therapy, PSA levels stabilize to a new baseline that is approximately 50% of the pre-treatment value. Results of subjects treated with TRADENAME for up to two years indicate this 50% reduction in PSA is maintained. Therefore, a new baseline PSA concentration should be established after 3 to 6 months of treatment with TRADENAME (see PRECAUTIONS: Effects on PSA and Prostate Cancer Detection).

**Hormone Levels:** In healthy volunteers, 52 weeks of treatment with dutasteride 0.5 mg/day (n = 26) resulted in no clinically significant change compared with placebo (n = 23) in sex hormone binding globulin, estradiol, luteinizing hormone, follicle-stimulating hormone, thyroxine (free T4), and dehydroepiandrosterone. Statistically significant, baseline-adjusted mean increases compared with placebo were observed for total testosterone at 8 weeks (97.1 ng/dL,  $p < 0.003$ ) and thyroid-stimulating hormone (TSH) at 52 weeks (0.4 mIU/mL,  $p < 0.05$ ). The median percentage changes from baseline within the dutasteride group were 17.9% for testosterone at 8 weeks and 12.4% for TSH at 52 weeks. In BPH patients treated with dutasteride in a large Phase III trial, there was a median percent increase in luteinizing hormone of 12% at 6 months and 19% at 12 months.

**Reproductive Function:** The effects of dutasteride 0.5 mg/day on reproductive function were evaluated in normal volunteers aged 18 to 52 (n = 26) throughout 52 weeks of treatment. Semen characteristics were evaluated at 3 timepoints and indicated no clinically meaningful changes in sperm concentration, sperm motility, or sperm morphology. A 0.8 mL (25%) mean decrease in ejaculate volume with a concomitant reduction in total sperm per ejaculate was observed at 52 weeks. These parameters remained within the normal range.

**CNS Toxicity:** In rats and dogs, repeated oral administration of dutasteride resulted in some animals showing signs of non-specific, reversible, centrally-mediated toxicity, without associated histopathological changes at exposure 425- and 315-fold the expected clinical exposure (of parent drug), respectively.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:**

**Carcinogenesis:** In a 2-year carcinogenicity study in B6C3F1 mice, at doses of 3, 35, 250, and 500 mg/kg/day for males and 3, 35, and 250 mg/kg/day for females. An increased incidence of benign hepatocellular adenomas was noted at 250 mg/kg/day (290-fold the expected clinical exposure to a 0.5 mg daily dose) in females only. Two of the three major human metabolites have been detected in mice. The exposure to these metabolites in mice is either lower than in humans or is not known.

In a 2-year carcinogenicity study in Han Wistar rats, at doses of 1.5, 7.5, and 53 mg/kg/day for males and 0.8, 6.3, and 15 mg/kg/day for females there was an increase in Leydig cell adenomas in the testes at 53 mg/kg/day (135-fold the expected clinical exposure). An increased incidence of Leydig cell hyperplasia was present at 7.5 mg/kg/day (52-fold the expected clinical exposure) and 53 mg/kg/day in male rats. A positive correlation between proliferative changes in the Leydig cells and an increase in circulating luteinizing hormone levels has been demonstrated with 5 $\alpha$ -reductase inhibitors and is consistent with an effect on the hypothalamic-pituitary-testicular axis following 5 $\alpha$ -reductase inhibition. At tumorigenic doses in rats, luteinizing hormone levels in rats were increased by 167%. In this study, the major human metabolites were tested for carcinogenicity at approximately 1 to 3 times the expected clinical exposure.

**Mutagenesis:** Dutasteride was tested for genotoxicity in a bacterial mutagenesis assay (Ames test), a chromosomal aberration assay in CHO cells, and a micronucleus assay in rats. The results did not indicate any genotoxic potential of the parent drug. Two major human metabolites were also negative in either the Ames test or an abbreviated Ames test.

**Impairment of Fertility:** Treatment of sexually mature male rats with dutasteride at doses of 0.05, 10, 50, and 500 mg/kg/day (0.1 to 110-fold the expected clinical exposure of parent drug) for up to 31 weeks resulted in dose- and time-dependent decreases in fertility, reduced cauda epididymal sperm counts (at 50 and 500 mg/kg/day), reduced weights of the epididymis, prostate and seminal vesicles, and microscopic changes in the male reproductive organs. The fertility effects were reversed by recovery week 6 at all doses, and sperm counts were normal at the end of a 14-week recovery period. The 5 $\alpha$ -reductase-related changes consisted of cytoplasmic vacuolation of tubular epithelium in the epididymides and decreased cytoplasmic content of epithelium, consistent with decreased secretory activity in the prostate and seminal vesicles. The microscopic changes were no longer present at

recovery week 14 in the low-dose group and were partly recovered in the remaining treatment groups. Low levels of dutasteride (0.6 to 17 ng/mL) were detected in the serum of untreated female rats mated to males dosed at 10, 50, or 500 mg/kg/ day for 29 to 30 weeks.

In a fertility study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5, and 30 mg/kg/day resulted in reduced litter size, increased embryo resorption and feminization of male fetuses (decreased anogenital distance) at doses of  $\geq 2.5$  mg/kg/ day (2- to 10-fold the clinical exposure of parent drug in men). Fetal body weights were also reduced at  $\geq 0.05$  mg/kg/day in rats ( $< 0.02$ -fold the human exposure).

**Pregnancy:** Pregnancy Category X (see CONTRAINDICATIONS). TRADENAME is contraindicated for use in women. TRADENAME has not been studied in women because preclinical data suggest that the suppression of circulating levels of dihydrotestosterone may inhibit the development of the external genital organs in a male fetus carried by a woman exposed to dutasteride.

In an intravenous embryo-fetal development study in the rhesus monkey (12/group), administration of dutasteride at 400, 780, 1325, or 2010 ng/day on gestation days 20 to 100 did not adversely affect development of male external genitalia. Reduction of fetal adrenal weights, reduction in fetal prostate weights, and increases in fetal ovarian and testis weights were observed in monkeys treated with the highest dose. Based on the highest measured semen concentration of dutasteride in treated men (14 ng/mL these doses represent 0.8 to 16 times (based on blood levels of parent drug) the potential maximum exposure of a 50-kg human female to 5 mL semen daily from a dutasteride-treated man, assuming 100% absorption. Dutasteride is highly bound to proteins in human semen ( $> 96\%$ ), potentially reducing the amount of dutasteride available for vaginal absorption.

In an embryo-fetal development study in female rats, oral administration of dutasteride at doses of 0.05, 2.5, 12.5, and 30 mg/kg/day resulted in feminization of male fetuses (decreased anogenital distance) and male offspring (nipple development, hypospadias, and distended preputial glands) at all doses (0.07- to 111-fold the expected male clinical exposure). An increase in stillborn pups was observed at 30 mg/kg/day, and reduced fetal body weight was observed at doses  $\geq 2.5$  mg/kg/day (15- to 111-fold the expected clinical exposure). Increased incidences of skeletal variations considered to be delays in ossification associated with reduced body weight were observed at doses of 12.5 and 30 mg/kg/day (56- to 111-fold the expected clinical exposure).

In an oral pre- and post natal development study in rats, dutasteride doses of 0.05, 2.5, 12.5, or 30 mg/kg/day were administered. Unequivocal evidence of feminization of the genitalia (i.e., decreased anogenital distance, increased incidence of hypospadias, nipple development) of F1

generation male offspring occurred at doses  $\geq 2.5$  mg/kg/day (14- to 90-fold the expected clinical exposure in men). At a daily dose of 0.05 mg/kg/day (0.05-fold the expected clinical exposure), evidence of feminization was limited to a small, but statistically significant, decrease in anogenital distance. Doses of 2.5 to 30 mg/kg/day resulted in prolonged gestation in the parental females and a decrease in time to vaginal patency for female offspring and decrease prostate and seminal vesicle weights in male offspring. Effects on newborn startle response were noted at doses greater than or equal to 12.5 mg/kg/day. Increased stillbirths were noted at 30 mg/kg/day.

Feminization of male fetuses is an expected physiological consequence of inhibition of the conversion of testosterone to DHT by  $5\alpha$ -reductase inhibitors. These results are similar to observations in male infants with genetic  $5\alpha$ -reductase deficiency.

In the rabbit, embryo-fetal study doses of 30, 100, and 200 mg/kg (28- to 93-fold the expected clinical exposure in men) were administered orally on days 7 to 29 of pregnancy to encompass the late period of external genitalia development. Histological evaluation of the genital papilla of fetuses revealed evidence of feminization of the male fetus at all doses. A second embryo-fetal study in rabbits at doses of 0.05, 0.4, 3.0, and 30 mg/kg/day (0.3- to 53-fold the expected clinical exposure) also produced evidence of feminization of the genitalia in male fetuses at all doses. It is not known whether rabbits or rhesus monkeys produce any of the major human metabolites.

**Nursing Mothers:** TRADENAME is not indicated for use in women. It is not known whether dutasteride is excreted in human milk.

**Pediatric Use:** TRADENAME is not indicated for use in the pediatric population. Safety and effectiveness in the pediatric population have not been established.

**Geriatric Use:** Of 2166 male subjects treated with TRADENAME in three clinical studies, 60% were 65 and over and 15% were 75 and over. No overall differences in safety or efficacy were observed between these subjects and younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

#### **ADVERSE REACTIONS:**

Adverse reactions were generally mild and transient. The most common adverse events leading to withdrawal in both treatment groups were associated with the reproductive system.

The data described below reflect exposure to TRADENAME in 2166 male subjects, including 1772 exposed for one year. Over 4300 male subjects with BPH were randomly assigned to receive placebo or 0.5-mg daily doses of TRADENAME in three identical, placebo-controlled Phase III treatment

studies. The population was aged 47 to 94 years (mean age 66 years) and greater than 90% Caucasian. A total of 267 subjects (6% of each treatment group) were withdrawn from the studies due to adverse experiences, usually associated with the reproductive system. Withdrawals due to adverse events considered by the investigator to have a reasonable possibility of being caused by the study medication occurred in 3% of the subjects receiving TRADENAME and in 2% of the subjects receiving placebo. Table 1 summarizes clinical adverse reactions that were reported by the investigator as drug-related in at least 1% of subjects receiving TRADENAME and at a higher incidence than subjects receiving placebo.

**Table 1: Drug-related Adverse Events\* Reported in  $\geq 1\%$  Subjects and More Frequently in the TRADENAME Group than the Placebo Group**

**Pivotal Studies Pooled**

<b>Adverse Event</b>	<b>Placebo (N = 2158)</b>	<b>TRADENAME (N = 2166)</b>
Impotence	59 (3%)	117 (5%)
Decreased libido	40 (2%)	74 (3%)
Ejaculation disorders	14 (<1%)	40 (2%)
Gynecomastia <sup>†</sup>	10 (<1%)	29 (1%)

**\* A drug-related adverse event is one considered by the investigator to have a reasonable possibility of being caused by the study medication. In assessing causality, investigators were asked to select from one of two options: reasonably related to study medication or unrelated to study medication.**

<sup>†</sup>Includes breast tenderness and breast enlargement

**Long-Term Treatment:** The incidence of sexual adverse events considered by the investigator to have a reasonable possibility of being drug-related decreased with duration of treatment; after the first 6 months of treatment the incidence of onset of impotence, decreased libido, ejaculation disorders or gynecomastia was <1% for subjects receiving either TRADENAME or placebo.

The adverse event profile for 677 subjects who were maintained on TRADENAME 0.5 mg/day for 24 months in one pivotal study was consistent with that observed after 12 months of treatment in the three studies combined. The incidence of onset of drug-related events was lower during the second



year of treatment compared with the first year of treatment, with the exception of gynecomastia (onset in 1% during first year and 2% during second year).

**OVERDOSAGE:** In volunteer studies, single doses of dutasteride up to 40 mg (80 times the therapeutic dose) for 7 days have been administered without adverse events or significant safety concerns. In clinical studies, doses of 5 mg daily have been administered to subjects for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5 mg.

There is no specific antidote for dutasteride. Therefore, in cases of suspected overdosage symptomatic and supportive treatment should be given as appropriate, taking the long half-life of dutasteride into consideration.

**DOSAGE AND ADMINISTRATION:** The recommended dose of TRADENAME is 1 capsule (0.5 mg) taken orally once a day. The capsules should be swallowed whole. TRADENAME may be administered with or without food.

No dosage adjustment is necessary for subjects with renal impairment or for the elderly (see **CLINICAL PHARMACOLOGY: Pharmacokinetics: Geriatric and Renal Impairment**). Due to the absence of data in patients with hepatic impairment, no dosage recommendation can be made (see **PRECAUTIONS: General**).

**HOW SUPPLIED:** TRADENAME Soft Gelatin Capsules 0.5 mg are oblong, opaque, dull yellow, gelatin capsules imprinted with “GX CE2” in red ink on one side packaged in bottles of 100 (NDC 0173-0712-00) with child-resistant closures and unit dose blister packs of 70 capsules (NDC 0173-0712-01).

**Storage and Handling:** Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Dutasteride is absorbed through the skin. TRADENAME Soft Gelatin capsules should not be handled by women who are pregnant or who may become pregnant because of the potential for absorption of dutasteride and the subsequent potential risk to a developing male fetus (see **CLINICAL PHARMACOLOGY: Pharmacokinetics, WARNINGS: Exposure of Women—Risk to Male Fetus, and PRECAUTIONS: Information For Patients and Pregnancy**).

Manufactured by:

NDA 21-319

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Beinheim, France for



GlaxoSmithKline

Research Triangle Park, NC 27709

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## **Patient Information**

### **TRADENAME (dutasteride) Soft Gelatin Capsules**

**TRADENAME is for use by men only.**

Read this information carefully before you start taking TRADENAME. Read the information you get with TRADENAME each time you refill your prescription. There may be new information. This information does not take the place of talking with your doctor.

#### **What is TRADENAME?**

TRADENAME is a medication to treat men who have symptoms of benign prostatic hyperplasia.

TRADENAME is not a treatment for prostate cancer. See the end of this leaflet for information about how TRADENAME works.

#### **Who should NOT take TRADENAME?**

- Women and children should not take TRADENAME. A woman who is pregnant or capable of becoming pregnant should not handle TRADENAME capsules. See **“What are the special warnings for women about TRADENAME?”**
- Do not take TRADENAME if you have had an allergic reaction to TRADENAME or any of its ingredients.
- Tell your doctor if you have liver problems. TRADENAME may not be right for you.

#### **What are the special warnings for women about TRADENAME?**

- Women should never take TRADENAME.
- Women who are pregnant or may become pregnant should not handle TRADENAME Capsules. If a woman who is pregnant with a male baby gets enough TRADENAME into her body after

swallowing it or through her skin after handling it, the male baby may be born with abnormal sex organs.

**What are the special precautions about TRADENAME?**

- Men treated with TRADENAME should not donate blood until at least 6 months after their final dose to prevent giving TRADENAME to a pregnant female through a blood transfusion.

**How should I take TRADENAME?**

- Take 1 TRADENAME capsule once a day.
- Swallow the capsule whole.
- You can take TRADENAME with or without food.
- If you miss a dose, you may take it later that day. Do not make up the missed dose by taking 2 doses the next day.
- You may find it helpful to take TRADENAME at the same time every day to help you remember to take your dose.

**What are the possible side effects of TRADENAME?**

The most common side effects of TRADENAME are impotence (trouble getting or keeping an erection), a decrease in libido (sex drive), and enlarged breasts. Also, some men may notice a decrease in the amount of semen they release during sex.

Talk with your doctor if you have questions about these and other side effects that you think may be related to taking TRADENAME.

**How should I store TRADENAME?**

TRADENAME is a soft gelatin capsule that may become soft and leak or may stick to other capsules if kept at high temperatures. Store TRADENAME capsules at room temperature of 77°F (25°C) or lower.

If your capsules are cracked or leaking, don't use them, and contact your pharmacist.

**General information about TRADENAME.**

- Do not use TRADENAME for a condition for which it was not prescribed.
- Do not share your TRADENAME.
- Ask your doctor about how often you should return for a visit to check your BPH.
- A blood test called PSA (prostate-specific antigen) is sometimes used to detect prostate cancer. TRADENAME will reduce the amount of PSA measured in your blood. Your doctor is aware of this effect and can still use PSA to detect prostate cancer in you.
- If you have questions about TRADENAME, ask your doctor or pharmacist. They can show you detailed information about TRADENAME that was written for healthcare professionals.

**How does TRADENAME work?**

Prostate growth is caused by a hormone in the blood called dihydrotestosterone (DHT).

TRADENAME lowers DHT production in the body, leading to shrinkage of the enlarged prostate in most men. Just as your prostate became large over a long period of time, reducing the size of your prostate and improving your symptoms will take time. While some men have fewer problems and symptoms after 3 months of treatment with TRADENAME, a treatment period of at least 6 months is usually necessary to see if TRADENAME will work for you.

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